

BRIEF DESCRIPTION OF THE FIGURES

[0017] FIG. 1 illustrates how an exemplary TAA presentation inducer construct may target an APC to TCDM or vice-versa. In this figure, the TAA presentation inducer construct is a bispecific antibody that binds to an ISR expressed on an APC, and to TAA1. Neoplastic cells give rise to exosomes and apoptotic/necrotic debris, also called tumor cell-derived material (TCDM) when they die. TCDM contains multiple TAAs, for example, TAA1-6, and neo-TAA1-2. Binding of the TAA presentation inducer construct to TAA1 and the ISR targets an innate immune cell such as an APC to the TCDM (or vice-versa). The APC may then internalize the TCDM to promote a polyclonal T cell response to one or more of TAA2-6 and neoTAA1-2. In some embodiments, the APC may also promote a polyclonal T cell response to TAA1 in addition to one or more of TAA2-6 and neoTAA1-2. The preceding description is for illustrative purposes and is not meant to be limited in any way to the type of TAA presentation inducer construct or type of number of TAAs, or other aspect of this Figure.

[0018] FIG. 2 illustrates exemplary general formats for TAA presentation inducer constructs in a bispecific antibody format. The constructs in FIGS. 2A, 2B, and 2D comprise an Fc, while the construct in FIG. 2C does not. FIG. 2A depicts a Fab-scFv format in which one antigen-binding domain is a Fab and the other is an scFv. FIG. 2B depicts a Fab-Fab format in which both antigen-binding domains are Fabs. This format is also referred to as full-size format (FSA). FIGS. 2C and 2D depict dual scFv formats in which two scFvs are either linked to each other (FIG. 2C) or linked to an Fc (FIG. 2D).

[0019] FIG. 3 illustrates additional exemplary formats for TAA presentation inducer constructs in a bispecific antibody format. The legend identifies different segments of the constructs and different fills (black versus grey) are used to represent segments that bind to distinct targets, or to represent a heterodimeric Fc. In some cases, these formats exhibit more than one valency for a target TAA or ISR. FIG. 3A depicts Format A: A_scFv_B_scFv_Fab, where Heavy Chain A includes an scFv and Heavy Chain B includes an scFv and a Fab. FIG. 3B depicts Format B: A_scFv_Fab_B_scFv, where Heavy Chain A includes an scFv and a Fab and Heavy Chain B includes an scFv. FIG. 3C depicts Format C: A_Fab_B_scFv_scFv, where Heavy Chain A includes a Fab and Heavy Chain B includes two scFvs. FIG. 3D depicts Format D: A_scFv_B_Fab_Fab, where Heavy Chain A includes an scFv and Heavy Chain B includes two Fabs. FIG. 3E depicts Format E: Hybrid, where Heavy Chain A includes a Fab and Heavy Chain B includes an scFv. FIG. 3F depicts Format F: A_Fab_CRT_B_CRT, where Heavy Chain A includes a Fab and calreticulin and Heavy Chain B includes calreticulin (CRT). FIG. 3G depicts Format G: A_Fab_CRT_B_CRT_CRT, where Heavy Chain A includes a Fab and calreticulin and Heavy Chain B includes two calreticulin polypeptides.

[0020] FIG. 4 illustrates exemplary formats for TAA presentation inducer constructs designed using split-albumin scaffolds, where “T” represents a trastuzumab scFv and “CRT” represents residues 18-417 of calreticulin. The formats of variants 15019, 15025, and 22923-22927 are illustrated.

[0021] FIG. 5 illustrates exemplary formats for TAA presentation inducer constructs designed using a heterodimeric Fc as a scaffold, where “T” represents a trastuzumab scFv

and “CRT” represents residues 18-417 of calreticulin. The formats of variants 22976-22982, 21479, 23044, 22275, and 23085 are illustrated. Black versus grey fill is used to distinguish individual Fc polypeptides of the heterodimeric Fc.

[0022] FIG. 6 depicts native target binding of constructs targeting HER2, ROR1, DECTIN1, CD40, or DEC205 transiently expressed in HEK293 cells. FIG. 6A depicts HER2 binding, FIG. 6B depicts ROR1 binding, FIG. 6C depicts dectin-1 binding, FIG. 6D depicts CD40 binding, and FIG. 6E and FIG. 6F both depict DEC205 binding.

[0023] FIG. 7 depicts native binding of constructs targeting mesothelin (MSLN) endogeneously expressed in H226 cells.

[0024] FIG. 8 depicts soluble binding of mouse anti-calreticulin (CRT) MAB3898 antibody from R&D Systems to TAA presentation inducer constructs containing a CRT-arm.

[0025] FIG. 9 illustrates TAA presentation inducer construct potentiation of tumor cell material phagocytosis.

[0026] FIG. 10 depicts the ability of TAA presentation inducer constructs to potentiate monocyte cytokine production in tumor cell co-cultures. FIG. 10A depicts the ability of construct Her2×CD40 (v18532) to potentiate cytokine production and FIG. 10B depicts the ability of construct Her2×CRT (v18535) to potentiate cytokine production.

[0027] FIG. 11 depicts the effect of TAA presentation inducer constructs on IFN γ production of MelanA-enriched CD8 $^{+}$ T cells. FIG. 11A depicts the effect in APCs incubated with OVCAR3 cells containing the MelanA peptide while FIG. 11B depicts the effect in APCs incubated with OVCAR3 cells containing a plasmid encoding a MelanA-GFP fusion protein.

DETAILED DESCRIPTION

[0028] Described herein is a multispecific tumor-associated antigen (TAA) presentation inducer construct that binds to at least one innate stimulatory receptor (ISR) expressed on an antigen-presenting cell (APC), and also directly binds to at least one first TAA. In some embodiments, the ISR may be a C-type lectin receptor, a tumor necrosis factor family receptor, or a lipoprotein receptor. The at least one first TAA may be an antigen that is physically associated with tumor cell-derived material (TCDM) comprising, or physically associated, with one or more other TAAs distinct from the first TAA. The TAA presentation inducer constructs can bind to the at least one ISR on the APC and to the at least one first TAA to induce a polyclonal T cell response to at least the one or more other TAAs physically associated with the TCDM. In one embodiment, the TAA presentation inducer construct can induce a polyclonal T cell response to the at least one first TAA as well as to the one or more other TAAs physically associated with the TCDM. The TAA presentation inducer construct may also promote TAA cross presentation in the APC. The at least one first TAA can act as a “handle” to facilitate polyclonal immunity to diverse TAAs in the presence of a TAA presentation inducer construct. In one embodiment, the TAA presentation inducer construct may be able to maintain the ability to induce a polyclonal T cell response to multiple TAAs as the TAA composition of the TCDM changes.

[0029] The TAA presentation inducer constructs may be used to treat cancer in a subject. The TAA presentation inducer described here may also be used to expand, activate,